REMARKS

Claims 14, 15, 17-19 and 21-23 are pending in the subject application. The Examiner previously deemed claims 1-13 and 24-36 withdrawn from consideration. Applicants have hereinabove cancelled claims 1-13 and 21-36 without disclaimer or prejudice to applicants' right to pursue the subject matter of this claim in a future application. In addition, applicants have hereinabove amended claim 15. Applicants maintain that none of the changes to the claims raise an issue of new matter.

In making this amendment, applicants neither concede the correctness of the Examiner's rejections, nor abandon their right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. Applicants maintain that this amendment raises no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 14, 15 and 17-19 will still be pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections have been overcome and respectfully request that the Examiner reconsider and withdraw same.

Rejection Under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 14, 15, 17-19 and 21-23 under 35

U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner stated that claims 14, 15 and 17-19 are method claims dependent on the identity of a compound determined to mimic the binding of the SML1 protein of SEQ ID NO:2 to the large subunit of ribonucleotide reductase.

The Examiner also stated that claims 21-23 are product claims dependent upon the identification of a fragment of Sml1 through the method of claim 14. The Examiner further stated that the specification provides a written description of Sml1 as SEQ ID NO:2 wherein said protein inhibits the activity of ribonucleotide reductase (pages 54 and 56). The Examiner further stated that the specification states on page 54, lines 19-24, "nonapeptides from the C terminus of Rnr2p or Rnr4p inhibited the in vivo yeast RNR assay to about the same extent with an Ic50 of 44 and 30 uM, respectively. In contrast the nonapeptides corresponding to the C terminus of Sml1p showed an inhibition with an IC50 of only about 300 uM". The Examiner further stated that thus, it appears that the nonapeptide derived from the C-terminus of Sml1 would not be capable of reducing the division rate of a cell by binding and effectively inhibiting RNR. The Examiner further stated that the specification does not provide a written description of

any fragments of Sml1 which are capable of reducing the division rate of a cell by means of mimicking the binding of full length Sml1 to ribonucleotide reductase. The Examiner further stated that one of skill in the art would reasonably conclude that applicant was not in possession of claims 21-23.

The Examiner stated that further, claims 14, 15 and 17-19 are method claims reliant on the identity of "a compound" which has been determined to mimic the binding of Sml1 to ribonucleotide reductase. The Examiner also stated that the term compounds encompasses a genus of molecules having highly variant structures. The Examiner further stated that the contemplation of a fragment of Sml1 as a mimic of ribonucleotide reductase binding by Sml1 does not adequately describe the claimed genus of "compounds" because said genus tolerates individual members having no structural relationship to Sml1. The Examiner further stated that one of skill in the art would reasonably conclude that applicant was not in possession of claims 14, 15 and 17-19 because a method claim which relied on a product which is not adequately described cannot itself be adequately described.

In response to the above rejection, but without conceding the correctness thereof, applicants point out that claims 21-23 have been canceled. Thus, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse. Applicants contend that the subject specification provides adequate written description evidencing applicants' possession of the claimed

invention at the time of filing.

First, applicants point out that claim 14 recites a compound that mimics the binding of SML1 protein to ribonucleotide reductase, not the binding efficiency of SML1 protein. Contrary to the Examiner's assertions, applicants describe a C-terminal nonapeptide of SML1 that does indeed inhibit the activity of ribonucleotide reductase (see page 58, lines 15-16). Applicants' results show that the nonapeptide has an IC_{50} of 300 uM. Therefore, the nonapeptide does inhibit the activity of ribonucleotide reductase.

In addition to the above mentioned fragment of SML1 protein, the specification sets forth at page 54, lines 14-24 that the C-terminal fragment of the Sml1 protein inhibits RNR activity by binding to the R1 subunit. This observation has been confirmed by a later published reference by Zhao et al. (*Molecular and Cellular Biology* 20(23): 9076-9083 (2000), attached hereto as **Exhibit A**). Specifically, applicants direct the Examiner to page 9080, column 2, lines 23-27 of Zhao et al. which states:

> "Thus, the N-terminal half of Sml1 (amino acids 2 to 50) is not required for RNR inhibition. Together with the mutagenesis data, these results clearly demonstrate that the C terminus is necessary and sufficient for the inhibitory role of Sml1."

Furthermore, the subject specification provides a very detailed description of methods for producing the compounds

used in claim 14. For example, peptidomimetics (see page 17, line 18 to page 19, line 12) and variants with biological activity (see page 21, lines 30-38) are described. In addition, methods of testing the interaction of the compound with ribonuclease reductase are also described (see page 52, line 30 to page 53, line 9).

Since the subject specification describes the portion of Sml1 protein that is required for binding to ribonuclease reductase and methods of making various compounds to be used in the methods of claims 14, 15 and 17-19, applicants maintain that the subject specification adequately describes the claimed invention.

In light of the above remarks, applicants maintain that claims 14, 15 and 17-19 satisfy the written description requirement of 35 U.S.C. §112, first paragraph and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Enablement

The Examiner rejected claims 14, 15, 17-19 and 21-23 under 35 U.S.C. §112, first paragraph, alleging that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation and with reasonable expectation of success.

The Examiner stated that in order to practice the method of

claim 14 one of skill in the art must be able to make a compound determined to mimic the binding of Sml1 protein to the large subunit of ribonucleotide reductase. The Examiner also stated that said compounds encompass organic compounds, inorganic compounds, lipids, peptidomimetics, a fragment of Sml1 protein or a synthetic compound as evidenced by claim 15. The Examiner further stated that in order to function as claimed in the reduction of cell division, said compounds must compete with Sml1 full length for binding to ribonucleotide reductase, and exert an inhibitory effect on ribonucleotide reductase. The Examiner further stated that the specification does not provide a single example of a compound which mimics the binding of Sml1 to ribonucleotide reductase, nor does the specification provide an example of a compound which binds to ribonucleotide reductase and exerts an inhibitory effect thereon. The Examiner further stated that the specification states that the Sml1 protein is about 200 times more efficient in inhibiting Rnr1 activity than the C-terminal nonapeptide (page 58, lines 27-29). The Examiner further stated that thus, it would be reasonably concluded that the nonapeptides would not be able to effectively elicit a decrease in the activity of ribonucleotide reductase necessary for limiting the growth of a cell. The Examiner further stated that the specification fails to provide an element of structure within a compound necessary for the reduction of the division rate of a cell, or specific examples of compounds which mimic the binding of Sml1 to ribonucleotide reductase and result in the inhibition of cell division. The Examiner further stated that given the lack of teachings in the specification regarding how to make compounds

which have the claimed characteristics, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to carry out the instant methods. The Examiner further stated that one of skill in the art would not be assured that a fragment of Sml1 exists which can bind to the large subunit of ribonucleotide reductase and reduce the division rate of a cell, because it would be necessary to efficiently bind to ribonucleotide reductase, and at the same time inhibit the activity of ribonucleotide reductase. The Examiner further stated that the specification has provided no assurances that such a fragment of Sml1 can have both characteristics of binding and inhibiting. The Examiner further stated that thus one of skill would be subject to undue experimentation without reasonable expectation of success in order to practice the broadly claimed methods and in order to make the pharmaceutical compositions as claimed.

In response to the above rejection, but without conceding the correctness thereof, applicants point out that claims 21-23 have been canceled. Thus, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse and maintain that the specification *in combination with* the prior art does indeed enable one skilled in the art to make and use the claimed invention. (*See, Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed.Cir. 1986), *cert. denied*, 480 U.S. 947 (1987)).

Again, applicants point out that claim 14 recites a compound

that mimics the *binding* of SML1 protein to ribonucleotide reductase, *not* the binding *efficiency* of SML1 protein. Contrary to the Examiner's assertions, applicants describe a C-terminal nonapeptide of SML1 that does indeed inhibit the activity of ribonucleotide reductase (see page 58, lines 15-16). Again, applicants' results show that the nonapeptide has an IC_{50} of 300 uM. Therefore, the nonapeptide does inhibit the activity of ribonucleotide reductase.

As discussed above, the specification also sets forth at page 54, lines 14-24 that the C-terminal fragment of the Sml1 protein inhibits RNR activity by binding to the R1 subunit. Again, this observation has been confirmed by Zhao et al. (Molecular and Cellular Biology 20(23): 9076-9083 (2000)).

Furthermore, as of applicants' filing date, i.e. March 22, 2001, methods of making and using peptidomimetics and protein variants were well known in the art. For example, on page 17, line 18 to page 19, line 12 applicants incorporate the teachings of U.S. Patent Numbers 5,446,128, 5,422,426, 5,440,013, which set forth methods of synthesizing peptidomimetics. In addition, on page 21, lines 30-38 applicants incorporate the teachings of Sambrook et al. which include methods for producing biologically active variants of proteins.

Moreover, applicants describe methods of testing the interaction of the compound with ribonuclease reductase (see page 52, line 30 to page 53, line 9).

For these reasons, applicants maintain that based on the guidance in the subject specification in combination with the prior art, one skilled in the art would be able to make and use the claimed invention without undue experimentation.

In light of the above remarks, applicants maintain that claims 14, 15 and 17-19 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

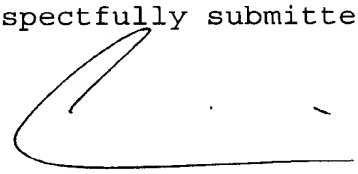
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the pending claims, i.e. claims 14, 15 and 17-19.

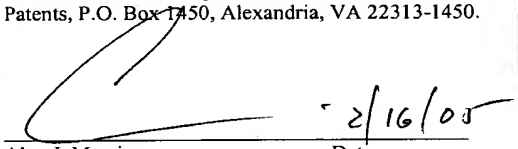
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



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